

# Health Effects of Air Pollutants: Sulfuric Acid, the Old and the New

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Data from exposure of experimental animals and human subjects to sulfuric acid presents a consistent picture of its toxicology. Effects on airway resistance in asthmatic subjects were well predicted by data obtained on guinea pigs. Sulfuric acid increases the irritant response to ozone in both rats and man. In donkeys, rabbits, and human subjects, sulfuric acid alters clearance of particles from the lung in a similar manner. These changes resemble those produced by cigarette smoke and could well lead to chronic bronchitis. Data obtained on guinea pigs indicate that very small amounts of sulfuric acid on the surface of ultrafine metal oxide aerosols produce functional, morphological, and biochemical pulmonary effects. Such particles are typical of those emitted from coal combustion and smelting operations. Sulfate is an unsatisfactory surrogate in existing epidemiology studies. Sulfuric acid measurement is a critical need in such studies.

I have chosen to narrow "The Health Effects of Air Pollutants" I was asked to address to "Sulfuric Acid, the Old and the New." At the International Symposium on Acid Aerosols at NIEHS, Judy Graham dedicated her summary remarks on the toxicology session to "the Amdur-Mead Guinea Pigs and to Donkey Gus and Donkey Ethel who started it all." When to these venerable beasts are added what I will call "Rich's Rabbits," the result is a triumvirate that makes a very strong case indeed for toxicology as a predictive science. The wall is covered with handwriting, some faded with age and some new, but the story it tells is extremely consistent. Along the way are a few ironies.

## Historical Background

Many toxicologists of my generation became so by accident. Sid Laskin's accident was the Manhattan Project; mine was Donora.

ASARCO had a zinc plant at Donora and they knew it put out sulfuric acid as did their western smelters. The air pollution incident in October 1948 so frightened them that they asked Professor Philip Drinker at Harvard to help them; Phil hired me. Whether by so doing he helped ASARCO has been, upon occasion, debated with vigor. The accident that turned me into a toxicologist, however, raises some interesting points.

The first is that 40 years ago at least one industry was well aware that sulfuric acid ( $\text{H}_2\text{SO}_4$ ) was among the pollutants they emitted. Second, they were concerned

enough about it after Donora that they measured it. To my first toxicology paper (1), results of which were other than they had hoped, they added a statement, "For the past 2 years Dr. M. D. Thomas and associates have been operating an automatic sulfuric acid analyzer in an industrial area. Visible amounts of sulfuric acid are known to occur and are largely uncontaminated by other aerosols. The concentration has never exceeded  $400 \mu\text{g}/\text{m}^3$ , while the average was less than 5% of this value," i.e.,  $20 \mu\text{g}/\text{m}^3$ . As historical data sets go, that would be an interesting one to see. The same paper also cited a 1950 Stanford Research Institute Report indicating that concentrations up to  $240 \mu\text{g}/\text{m}^3$  had been found in the Los Angeles area. Although these data were intended to indicate how low atmospheric levels were, they are of interest now because they give a clue of how high they were.

By 1961, things were improving in California as suggested by another more limited data set from Thomas, then at Stanford Research Institute, shown in Table 1 (2). It shows my average of his daily measurement values for the period and the low and high days. In a recent survey of measurement of acidic sulfur aerosols by Lioy and Lipmann (3), the first Los Angeles data they found was from 1979 and reported a 4-hr maximum value of  $11 \mu\text{g}/\text{m}^3$ . I

Table 1.  $\text{H}_2\text{SO}_4$ , 1961.<sup>a</sup>

Value	$\text{H}_2\text{SO}_4$ , $\mu\text{g}/\text{m}^3$	
	El Segundo	Los Angeles
Average	17.5	33.1
Low	6.4	19.2
Maximum	39.2	50.4

<sup>a</sup>Data from Thomas (2).

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am not sure when or why the measurement of  $\text{H}_2\text{SO}_4$  became unstylish, but it did. To my way of thinking, that is an irony of major impact.

In 1952, 4000 excess deaths were attributed to the London fog. Another irony is that in 1936, Firket (4) predicted that if an incident such as the one in the Meuse Valley in 1930 were to occur in London, 3200 deaths would result. Ironically, daily measurements of  $\text{H}_2\text{SO}_4$  were not started in London until 1963, 11 years after the fog. Toxicology had murmured 6 years before that  $\text{H}_2\text{SO}_4$  was a more potent irritant than sulfur dioxide ( $\text{SO}_2$ ), at least in acute exposure of guinea pigs (3). This murmur about comparative toxicity was to be strengthened in 1975 by publication of the Hazelton Laboratory data on 2-year exposure to monkeys (5). Moderate to severe histopathology and moderate alteration of distribution of ventilation were produced by  $480 \mu\text{g}/\text{m}^3$   $\text{H}_2\text{SO}_4$  ( $0.54 \mu\text{m}$ ), whereas no effects were seen from 1 ppm  $\text{SO}_2$ , which contains 10 times as much sulfur.

Ito and Thurston, here at NYU, are currently examining the London data set, which does exist from 1963 to 1972 (6). By examining the relationship of  $\text{H}_2\text{SO}_4$  to the pollution factors that had also been measured earlier, they may be able to develop formulae to predict what exposures to  $\text{H}_2\text{SO}_4$  were in the period when direct data are not available. Table 2, derived from their paper, shows the levels of  $\text{H}_2\text{SO}_4$  that were observed. Toxicology is now making murmurings about repeated exposures to the maximum levels actually measured, and levels in the 1950s were obviously much higher. When Ito and Thurston mesh their predictions with the existing mortality data for those earlier years, toxicology gives them very good odds of having high correlation coefficients.

## Pulmonary Mechanics: Guinea Pigs and Human Subjects

To start examining how the data all fit together, let us go first from guinea pigs to man. Back in 1971 (7), I went one rung further up the extrapolative ladder than usual and said that if my guinea pigs were analogous to anything at all, it was to the sensitive segment of the population. As data on the exposure of asthmatic subjects began to appear in the 1980s, first on  $\text{SO}_2$ , then on  $\text{H}_2\text{SO}_4$ , the extrapolation seemed valid. Table 3 makes the case for

Table 3. From guinea pig to man.

Subject	Response
Guinea pig	100–1000 $\mu\text{g}/\text{m}^3$ causes dose-related increase in airway resistance (8)
Normal humans	1000 $\mu\text{g}/\text{m}^3$ causes no response
Adult exercising asthmatics	450–1000 $\mu\text{g}/\text{m}^3$ causes dose-related increase in airway resistance; 100 $\mu\text{g}/\text{m}^3$ causes no response (9)
Adolescent exercising asthmatics	100 $\mu\text{g}/\text{m}^3$ causes increase in airway resistance (10)

$\text{H}_2\text{SO}_4$ . Guinea pigs had responded in a dose-related way to 100 to 1000  $\mu\text{g}/\text{m}^3$  (8), whereas a number of studies of normal subjects had shown no response to 1000  $\mu\text{g}/\text{m}^3$ . Adult, exercising asthmatics responded in a dose-related way to 450 to 1000  $\mu\text{g}/\text{m}^3$  but not to 100  $\mu\text{g}/\text{m}^3$  (9). Koenig (10), using the more sensitive adolescent subjects, found that 100  $\mu\text{g}/\text{m}^3$  caused increased airway resistance. At the Symposium on Acid Aerosols, she reported that a concentration of 68  $\mu\text{g}/\text{m}^3$  produced a lesser, but still statistically significant increase in airway resistance in these subjects (11). Her earlier work with  $\text{SO}_2$  (12) combines with these data to make a statement about comparative toxicity. The response to 100  $\mu\text{g}/\text{m}^3$  was similar to that produced for the same protocols and similar subjects by 1300  $\mu\text{g}/\text{m}^3$  (0.5 ppm)  $\text{SO}_2$ . The story is still consistent.

Koenig showed another interesting piece of data (11). At 0.1 ppm,  $\text{SO}_2$  did not produce a response in her subjects; however, when it was given combined with 68  $\mu\text{g}/\text{m}^3$   $\text{H}_2\text{SO}_4$  the response was greater than with the acid alone. This is important because the two occur together in pollution situations. Table 4 shows data on combined exposures to  $\text{H}_2\text{SO}_4$  and  $\text{SO}_2$  in guinea pigs and human subjects. The guinea pig data on increases in airway resistance indicate an additive effect (13). The data on human subjects use another criterion, decrease in tidal volume, and were only 10-min exposures; however, once again the response is additive. In this case, the guinea pig data came 20 years after the human data, but their message is the same. Comparative toxicity also comes through consistently in both species.

Table 2. Historical London daily aerosol acidity data, winter months (November–February), 24-hr average.<sup>a</sup>

Year	$\text{H}_2\text{SO}_4$ , $\mu\text{g}/\text{m}^3$	
	Average	Maximum
63/64	10.4	134.1
64/65	7.3	42.2
65/66	7.5	24.3
66/67	5.2	22.5
67/68	7.6	25.3
68/69	6.0	17.0
69/70	4.8	19.0
70/71	3.3	29.7
71/72	4.5	13.7

<sup>a</sup>Data from Ito and Thurston (6).

Table 4. Joint toxic action of  $\text{SO}_2$  and  $\text{H}_2\text{SO}_4$  (MMD  $1 \mu\text{m}$ ).

$\text{H}_2\text{SO}_4$ , $\mu\text{g}/\text{m}^3$	$\text{SO}_2$ , ppm	Number of subjects	Raw increase cm $\text{H}_2\text{O}/\text{mL}/\text{sec}$	Decrease in tidal volume, %
Guinea pigs <sup>a</sup>				
100	—	9	0.07	
—	0.2	15	0.10	
100	0.2	30	0.18	
Humans <sup>b</sup>				
120	—	5		5.0
—	0.6	5		6.1
120	0.6	5		14.0
—	1.0	5		12.1
120	1.0	5		15.7

<sup>a</sup>1-hr exposure (13).

<sup>b</sup>10-min exposure (30).

## Joint Toxicity of $\text{H}_2\text{SO}_4$ and $\text{O}_3$ : Rats, Guinea Pigs, and Human Subjects

Another very interesting joint toxic action is emerging from Last's group at the University of California at Davis (14), in this case  $\text{H}_2\text{SO}_4$  and ozone ( $\text{O}_3$ ). Rats are quite insensitive to  $\text{H}_2\text{SO}_4$ , but the addition of  $\text{H}_2\text{SO}_4$  to  $\text{O}_3$  produced a greater response than  $\text{O}_3$  alone as measured by collagen synthesis and other criteria. Ammonium sulfate can produce a similar effect but only at much higher concentrations.  $\text{H}_2\text{SO}_4$  potentiates the response to  $\text{O}_3$  at concentrations as low as  $40 \mu\text{g}/\text{m}^3$ , the lowest Last has tested. His findings are very important because these two pollutants occur together.

Once again, toxicology data on animals and human subjects are completely consistent. In 1975, Haszucha and Bates (15) reported synergism between  $\text{O}_3$  and  $\text{SO}_2$  in human subjects and hypothesized that perhaps  $\text{H}_2\text{SO}_4$  was formed in the lung. The Amdur-Mead guinea pig system indicated that this was highly unlikely (16). The synergism was weak to nonexistent in studies by Hackney at Rancho Los Amigos (17). Those chambers, like mine, did not contain sulfate or  $\text{H}_2\text{SO}_4$ . Retrospective studies (17) of the original Montreal chambers indicated the presence of up to  $200 \mu\text{g}/\text{m}^3$  sulfate, which would presumably have been  $\text{H}_2\text{SO}_4$ . Although they came along 10 years after the human subjects, we can add "Jerry's rats" to our community of predictive beasts; it would be advisable to pay them close attention.

## Particle Clearance: Donkeys, Rabbits, and Human Subjects

Let us look next at the superb contribution NYU has made to the  $\text{H}_2\text{SO}_4$  story. They give us completely comparable data on animals and human subjects when this is ethical and possible in a way that gives strong extrapolative importance to their animal data when similar data on human subjects are impossible to obtain. A single 1-hr exposure of donkeys to  $100$  to  $1000 \mu\text{g}/\text{m}^3$   $\text{H}_2\text{SO}_4$  caused alterations in bronchial mucociliary clearance at concentrations above  $200 \mu\text{g}/\text{m}^3$ . A single 1-hr exposure of human subjects to similar concentrations also altered clearance. Donkeys exposed to  $100 \mu\text{g}/\text{m}^3$   $\text{H}_2\text{SO}_4$  1 hr/day, 5 days/week for 6 months showed altered clearance that persisted for 3 months after the end of exposure. Such changes could lead on to chronic bronchitis.

Other NYU data shows that in acute exposure to cigarette smoke, donkeys and humans react in a similar manner; furthermore, the response to cigarette smoke and to  $\text{H}_2\text{SO}_4$  is alike in both species. Donkeys who smoked 30 cigarettes 3 times/week for about 30 weeks showed altered clearance persisting for several months. It is not possible to expose human subjects to  $\text{H}_2\text{SO}_4$  daily for 6 months, but some of them expose themselves to cigarette smoke for far longer periods and many end up with chronic bronchitis. The donkey data send a clear message, discussed in detail in the recent paper of Lippman et al. (18).

More recent work with rabbits has done much to strengthen this message. The acute effects of a single 1-hr exposure to  $\text{H}_2\text{SO}_4$  are very similar with an acceleration at low doses ( $100 \mu\text{g}/\text{m}^3$  in human subjects and 200 to  $300 \mu\text{g}/\text{m}^3$  in rabbits) and a slowing at high concentrations ( $1000 \mu\text{g}/\text{m}^3$  in both species) (18). Subchronic exposures of 1 hr/day, 5 days/week for 4 weeks,  $250 \mu\text{g}/\text{m}^3$  orally or  $500 \mu\text{g}/\text{m}^3$  nasally caused increased epithelial thickness of small conducting airways and an increased number of airways containing epithelial secretory cells. Nasal exposure to  $250 \mu\text{g}/\text{m}^3$  increased the number of epithelial secretory cells in the smallest airways. All groups showed accelerated clearance during the 23-week postexposure follow-up (19). These changes all point toward the onset of chronic bronchitis.

In a more recent exposure to  $250 \mu\text{g}/\text{m}^3$  for 1 hr/day, 5 days/week for a year (18,19), bronchial mucociliary clearance was slowed during exposure and became even slower in the 3-month follow-up. Early alveolar clearance was accelerated during the exposure. Secretory cell density was elevated in some airways at 4 months and in all lung airways at 8 months. At 12 months the increased density remained in small and mid-sized airways, but not in the large. Once again, these changes could predict chronic bronchitis. Partial recovery occurred at 3 months postexposure. The finding of increased airway reactivity at 4.8 and 12 months fits with the observation of increased incidence of wheeze in individuals exposed to  $\text{H}_2\text{SO}_4$  from power plant emissions ( $\text{SO}_2$  was the surrogate).

## $\text{H}_2\text{SO}_4$ on Sulfur of Combustion on Aerosols

My own group at MIT has been examining the effects of  $0.05 \mu\text{m}$  zinc oxide ( $\text{ZnO}$ ) particles that carry a layer of  $\text{H}_2\text{SO}_4$ . We now have the quantitative speciation of sulfur on the aerosol (20) without which rational interpretation of pulmonary response is not possible. These particles are completely analogous to primary emissions from smelters and coal combustors. We have known such particles were out there, but it took a decade of closely coordinated interdisciplinary research to finally study them. Because the  $\text{H}_2\text{SO}_4$  reaches the deep lung as a readily available surface layer, it produces a response at very low concentrations. Another very critical aspect of our data is the fact that functional, morphological, and biochemical responses to these ultrafine acid-coated aerosols closely resemble the responses to  $\text{O}_3$ .

We find that a single 3-hr exposure to  $50 \mu\text{g}/\text{m}^3$   $\text{H}_2\text{SO}_4$  as a surface layer produces decrements in lung volumes and pulmonary diffusing capacity that persist for 48 to 72 hr (21). There is centriacinar morphological damage and evidence of pulmonary edema and increased epithelial permeability. Repeated daily 3-hr exposures for 5 days (22) to  $20 \mu\text{g}/\text{m}^3$  produce cumulative effects on lung volumes, diffusing capacity, increases in protein and neutrophils in pulmonary lavage fluid, and increases in lung weight/body weight ratio that are dose-related. A single 1-hr exposure to  $20 \mu\text{g}/\text{m}^3$  increases airway reactivity. Our

plans include additional studies of similar particles produced by controlled combustion of coal. I offer the thought that particles such as these were the major causative agent in the increased wheeze noted by Schenker et al. (23) in a rural population in the Chestnut Ridge area of western Pennsylvania living downwind from coal combustion effluents. His surrogate was SO<sub>2</sub>.

## Epidemiologic Surrogates

Epidemiology of the SO<sub>2</sub> particulate complex has bogged itself down with surrogates for H<sub>2</sub>SO<sub>4</sub>. As far back as 1961 (24), sulfate proved to be the best. Ozkaynak and Spengler (25) found that daily mortality correlated better with sulfate than with other surrogates. Bates (26) found hospital admissions for asthma correlated better with sulfate than with other surrogates. Another observation was that elevated O<sub>3</sub> appeared to contribute to the effect of sulfate; please remember "Jerry's rats."

As Lippmann (27) so well put it, "the fact that sulfate is a better surrogate for the active component of FP than FP, IP, or TSP still does not make it a good one." In a strong chorus, guinea pigs (28), donkeys (18), rabbits (18,19), rats (14), asthmatic human subjects (9), a polite male toxicologist (27), and a less polite female toxicologist (29) have all been for at least 10 years crying out that sulfate is a terrible surrogate.

When the Six-Cities Study was started, I was still at Harvard, so it was temptingly easy to offer unsolicited advice. I did: "Whatever else you do, make measurement of sulfuric acid your top priority. It is the component of the SO<sub>x</sub>-particulate complex that will give you clear-cut association with health effects you measure." As a toxicologist, I do not understand completely why it was possible to measure H<sub>2</sub>SO<sub>4</sub> in the 1950 to 1960s era, but it then presumably became an insoluble research problem. Spengler showed that they now know how to measure H<sub>2</sub>SO<sub>4</sub> (29). It is hoped that it will be in wide use by the time the Six-Cities becomes 24 cities. Many surrogated cities would surely make the animals weep that they had died in vain and make the toxicologists weep that they had worked in vain.

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## REFERENCES

1. Amdur, M. O., Schulz, R. Z., and Drinker, P. Toxicity of sulfuric acid to guinea pigs. *Arch. Ind. Hyg. Occup. Med.* 5: 318-329 (1952).
2. Thomas, M. O. Sulfur dioxide, sulfuric acid aerosol and visibility in Los Angeles. *Int. J. Air Water Pollut.* 6: 443-454 (1962).
3. Liou, P. J., and Lippmann, M. Measurement of exposure to acidic sulfur aerosols. In: *Aerosols: Research, Risk Assessment and Control Strategies* (S. D. Lee, T. Schneider, L. D. Grant, and P. J. Verherk, Eds.), Lewis Publishers, Chelsea, MI, 1986, pp. 743-752.
4. Firket, J. Fog along the Meuse Valley, *Trans. Faraday Soc.* 32: 1102-1197 (1936).
5. Alarie, Y. C., Krumm, A. A., Busey, W. M., Ulrich, C. W., and MacFarland, H. N. Long-term continuous exposure to sulfur dioxide, sulfuric acid mist, fly ash, and their mixtures. Results of studies in monkeys and guinea pigs. *Arch. Environ. Health* 30: 254-262 (1975).
6. Ito, K., and Thurston, G. D. Characterization and reconstruction of historical London, England, acidic aerosol concentrations. *Environ. Health Perspect.* 79: 35-42 (1989).
7. Amdur, M. O. The impact of air pollutants on physiologic responses of the respiratory tract. *Proc. Am. Philos. Soc.* 114(1): 3-8 (1970).
8. Amdur, M. O., Dubriel, M., and Creasia, D. A. Respiratory response of guinea pigs to low levels of sulfuric acid. *Environ. Res.* 15: 418-423 (1978).
9. Utell, M. J., Morrow, P. E., and Hyde, R. W. Airway reactivity to sulfate and sulfuric acid aerosols in normal and asthmatic subjects. *J. Air Pollut. Control Assoc.* 34: 931-935 (1984).
10. Koenig, J. Q., Pierson, W. E., and Horike, M. The effects of inhaled sulfuric acid on pulmonary function in adolescent asthmatics. *Am. Rev. Respir. Dis.* 128: 221-225 (1983).
11. Koenig, J. Q., Covert, D. S., and Pierson, W. E. The effects of inhalation of acidic compounds on pulmonary function in allergic adolescent subjects. *Environ. Health Perspect.* 79: 173-178 (1989).
12. Koenig, J. Q., Pierson, W. E., Horike, M., and Frank, R. Effects of SO<sub>2</sub> plus NaCl aerosol combined with moderate exercise on pulmonary function in asthmatic adolescents. *Environ. Res.* 25: 340-348 (1981).
13. Amdur, M. O. 1974 Cummings Memorial Lecture: The Long Road from Donora. *Am. Ind. Hyg. Assoc. J.* 35: 589-597 (1974).
14. Warren, D. L., and Last, J. A. Synergistic interaction of ozone and respirable aerosols on rat lungs. III. Ozone and sulfuric acid. *Toxicol. Appl. Pharmacol.* 88: 203-216 (1987).
15. Hazucha, M., and Bates, D. V. Combined effect of ozone and sulphur dioxide on human pulmonary function. *Nature* 257: 50-51 (1975).
16. Amdur, M. O., Ugro, V., and Underhill, D. W. Respiratory response of guinea pigs to ozone alone and with sulfur dioxide. *Am. Ind. Hyg. Assoc. J.* 39: 958-961 (1978).
17. Bell, K. A., Linn, W. S., Hazucha, M., Hackney, J. D., and Bates, D. V. Respiratory effects of exposure to ozone plus sulfur dioxide in Southern Californians and Eastern Canadians. *Am. Ind. Hyg. Assoc. J.* 38: 696-706 (1977).
18. Lippmann, M., Gearhart, J. M., and Schlesinger, R. B. Basis for a particle size-selective TLV for sulfuric acid aerosols. *Appl. Ind. Hyg.* 2: 88-199 (1987).
19. Schlesinger, R. B., Naumann, B. D., and Chen, L. C. Physiological and histological alterations in the bronchial mucociliary clearance system of rabbits following intermittent oral or nasal inhalation of sulfuric acid mist. *J. Toxicol. Environ. Health* 12: 441-465 (1983).
20. Amdur, M. O., Chen, L. C., Gutty, J., Lam, H. F., and Miller, P. D. Speciation and pulmonary effects of acidic SO<sub>x</sub> formed on surface of ultrafine zinc oxide aerosols. *Atmos. Environ.* 22: 557-560 (1988).
21. Amdur, M. O., Sarofin, A. F., Neville, M., Quann, P. J., McCarthy, J. F., Elliott, J. F., Lam, H. F., Rogers, A. E., and Conner, M. W. Coal combustion aerosols and SO<sub>2</sub>: An interdisciplinary analysis. *Environ. Sci. Technol.* 20(2): 138-145 (1986).
22. Amdur, M. O., and Chen, L. C. Furnace generated acid aerosols: Speciation and pulmonary effects. *Environ. Health Perspect.* 79: 147-150 (1989).
23. Schenker, M. B., Speizer, F. E., Samet, J. M., Gruhl, J., and Batterman, S. Health effects of air pollution due to coal combustion in the Chestnut Ridge region of Pennsylvania: Results of cross-sectional analysis in adults. *Arch. Environ. Health* 38: 325-330 (1983).
24. Dohan, F. C. Air pollutants and incidence of respiratory disease. *Arch. Environ. Health* 3: 387-395 (1961).
25. Ozkaynak, H., and Spengler, J. D. Mortality and morbidity effects resulting from population exposures to airborne particles. *Environ. Health Perspect.* 63: 45-55 (1985).
26. Bates, D. V. Relation of hospital admissions to pollutant levels. Presented at the International Epidemiology Association Meeting, August 1984, Vancouver, British Columbia.
27. Lippmann, M. Airborne acidity: Estimates of exposure and human health effects. *Environ. Health Perspect.* 63: 63-70 (1985).
28. Amdur, M. O., Bayles, J., Ugro, V., and Underhill, D. W. Compar-

- tive irritant potency of sulfate salts. *Environ. Res.* 16: 1-8 (1978).
29. Amdur, M. O. Toxicological guidelines for research on sulfur oxides and particulates. In: *Proceedings of the Fourth Symposium on Statistics and the Environment* (R. H. Foote, Ed.), March 3-5, 1976 American Institute on Statistics, 1977, pp. 48-55.
30. Amdur, M. O. Response of the human subjects to combinations of  $\text{SO}_2$  and  $\text{H}_2\text{SO}_4$ . Presented at the American Industrial Hygiene Assoc. Meeting, Chicago, IL, May 1954.
31. Spengler, J. D., Keeler, G. J., Koutrakis, P., Ryan, P. B., Raizenne, M., and Franklin, C. A. Exposures to acidic aerosols. *Environ. Health Perspect.* 79: 43-51 (1989).